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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,129	08/05/2002	David Norman Wells	4070.000300	1451

23720 7590 04/13/2006

WILLIAMS, MORGAN & AMERSON
10333 RICHMOND, SUITE 1100
HOUSTON, TX 77042

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,129	WELLS, DAVID NORMAN	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46 and 49-66* is/are pending in the application.

4a) Of the above claim(s) *34-46,49-55,57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,56 and 59-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/5/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 1/9/06, has been entered. Claims 1-46 and 49-66 are pending; claims 34-46, 49-55, 57, 58 are withdrawn; claims 1-33, 56, 59-66 are under current examination

Non-Compliant Amendment

Applicants' argue that the claims in question were properly identified under the modified rules. Applicants' have provided a new set of claims.

The amendment to the claims is considered compliant. The Examiner notes that the Notice of Non-Compliant Amendment clearly states that the remarks state the cancellation of claims 16-55. This is also evident on the first page of the claim Amendment (see #1.1). Thus, it was unclear from this version of claims, if the claims were cancelled or withdrawn, as Applicants' remarks were contrary to what the status identifier stated.

Election/Restrictions

Claims 34-46, 49-55, 57 and 58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/6/06.

Applicant's election with traverse of Group I in the reply filed on 1/6/06 is acknowledged. The traversal is on the ground(s) that :

1) the restriction is improper because no lack of unity was imposed during the PCT phase of prosecution; 2) the restriction is incomplete, because there is no indication of classification/separate status of each group by, for example, class and subclass, citing MPEP §814 and 3) that the restriction is

inaccurate because claim 56 was not pending at the time of restriction, and claim 52 has not been identified with an appropriate group; 4) that because the International Examining Authority found no lacking in unity of invention, Applicants argue that the imposition of Restriction Groups 4-12 represent a severe economic burden on Applicants, and Applicants' propose their own restriction, with 7 groups.

This is not found persuasive. The Examiner responds as follows: 1) the Examiner is unaware of any rule that states that if no lack of unity is found during the PCT phase, that an Examiner cannot determine lack of unity in the corresponding 371 case, each case is determine upon its own merits; 2) the restriction is not incomplete for lack of classification. The section that Applicants' are pointing to (§814) is not directed to 371 cases, but to cases filed under 35 USC §111. This application is filed under 37 USC §371, which the MPEP states should be considered, with regard to lack of unity, in Chapter 1800. See MPEP §801. There is no requirement for classification in a lack of unity. MPEP §1893.03(d) details the requirements for Unity of Invention, particularly, that the Examiner must explain why each group lacks unity, and does not have a single, general inventive concept. 3) Claim 56 should not have been grouped in Group XV, as Applicants have correctly pointed out that it was not currently pending. Group XV should only consist of claim 55. Furthermore, with regard to claim 52, it is obvious from the restriction requirement, that claim 52 should be groups with each of Groups IV-XII, as claim 52 recites each of the diseases that is recited in each of these groups.

The Examiner agrees to rejoin Groups I-II (claims 1-33, 56, 59-66), which is directed to methods of nuclear transfer and producing cloned animals and embryos. This is in accordance with 37 CFR 1.47, which provides for a product, manufacture of the product, and use of the product. Instantly, this would refer to nuclear transfer embryos (product) by methods

of nuclear transfer (manufacturing) and producing cloned animals (use of the product). The Examiner does not agree with Applicants' "Proposed Restriction Requirement", with regard to Applicants' Group IV, particularly, because each disease is not considered to be a species. Each disease has its own etiology and specific considerations. A species is wherein different embodiments could fall within the scope of a generic claim (see MPEP §806.04). This is not the instant case – each disease is separate and distinct, and do not share any characteristics that would lead one to reasonably determine that they would fall within a particular genus. For example, neurological disorders and diabetes have different modes of action; have different causes, effects, and treatment for each would require a separate and distinct consideration.

Newly added claims 57 and 58 are withdrawn. These claims are directed to producing embryonic cells from a blastocyst, and establishing a cell line from the cells. These claims are found to fall within the invention of Group III of the Restriction requirement (methods of producing an embryonic cell line).

Information Disclosure Statement

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be

listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

The information disclosure statement filed 8/5/02 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The information referred to therein has not been considered because the cited non-patent references have not been supplied. The only reference that has been supplied and considered is Reference B1 (WO 9946982)n and the international search report (Reference C34).

Claim Objections

Claim 10 is objected to because of the following informalities: the claim recites "A method as claimed in claim 1." However, claim 1 is directed to one method, therefore, it is suggested claim 10 should be amended to reflect this, by reciting, "The method ...". Claims 17-18, 25-27 are similarly objected to because they recite "A method....".

Claim 24 is objected to because of the following: the claim recites "optionally breeding from the non-human animal." This is grammatically incorrect, as one would breed the animal, not breed from the animal.

Claim 31 is objected to because of the following informalities: The claim appears to be incomplete, because it recites "a transgenic bovine or" and the sentence is left unfinished. Appropriate correction is required.

Claim 32 is objected to because of the following: the claim is grammatically incorrect and recites "improve" resistance in line 5 of the claim. It appears this should read improved resistance..

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 20, 22, 23, 28, 29 and 33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to reconstituted non-human embryo (claim 20, 22, 23), cloned non-human animals (claims 28, 29) and offspring and descendents of the animals (claim 33). The claims read on products of nature, particularly naturally occurring embryos, animals, and offspring/descendents of the animals. Although the claims recite the term "reprogrammed" or "cloned", these terms fail to distinguish the cloned animals or embryos from naturally occurring animals or embryos. Furthermore, claim 23 includes human embryos. As such, the claims encompass non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33, 56, 59-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) Methods of nuclear transfer, comprising selecting and segregating non-primate mammalian G1 cells from a proliferating or non-proliferating population of non-primate mammalian donor cells, and transferring the nucleus of the segregated cell into an enucleated, non-primate mammalian oocyte,

2) Methods of producing cloned non-primate mammalian embryos said methods of nuclear transfer,

3) Reconstituted non-primate mammalian embryos produced by said methods,

4) Methods of cloning a non-primate mammal, comprising the steps of producing a non-primate mammalian embryo, as recited above, transferring the embryo to a non-primate, mammalian surrogate mother of the same species, allowing the non-primate embryo to develop to produce a live born non-primate mammal,

5) Non-primate mammals produced by said methods.

The specification does not reasonably provide enablement for the breadth of the claims, which is directed to utilizing, from any species, any G1 cell, and any oocyte, in nuclear transfer methods, to produce an animal embryo, from any species, and further allowing the animal embryo to develop into a cloned, live born animal of any species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention/Breadth of the claims. The claims are directed methods of nuclear transfer (NT) to produce cloned embryos, and methods of producing cloned animals by NT methods. The breadth of the claims encompasses using any donor cell, any recipient cell, in the NT methods, to produce any species of animal.

Guidance of the Specification/The Existence of Working Examples. The working examples in the specification are directed to comparing the *in vitro* development of NT embryos using either G1 or G0 cells (Example 1); where the G1 cells were induced to enter quiescence by serum deprivation and the G1 cells are produced by identifying mitotic cells, and then exposed to an enzymatic solution, wherein the cell cycle phase of individual cell types or cell lines can be identified by, for example BrdU labeling of a sample of the cells (pages 15-16); the specification further teaches utilizing two follicular donor cells synchronized in either G0 or G1 for nuclear transfer and found no difference in the *in vitro* development of cloned embryos using either cell types (Example 2). The specification teaches comparing the *in vivo* development of the NT embryos of Example 2, and found that there was a higher tendency for embryo survival with cloned embryos using G0 cells than G1, but was not of statistical significance (Example 3). The specification teaches using two synchronized cell lines of female skin fibroblasts (one obtained at late puberty, and one at early onset of puberty) as nuclear donors, and found no significant difference between *in vitro* and *in vivo* development of the embryos resulting from NT (Example 4). The specification teaches using two lines of adult skin fibroblasts synchronized in either G0 or G1, and analysis of the *in vitro* and *in vivo* development of NT embryos produced from both cell lines, concluding that there was no difference in efficiency of development to blastocyst stage (Example 5, p. 30, lines 17-23). The

specification teaches using genetically modified bovine fetal fibroblast cells, synchronized in either G0 or G1, and analysis of the *in vitro* and *in vivo* development of the resultant NT embryo, and conclude that development to blastocyst stage was significantly less when utilizing a G1 cell, compared to a G0 cell (Example 6, and Table 5). Example 7 compares using late G1 phase, senescent cells, and found that development to blastocyst stage of these NT embryos was much lower than when using G0 or G1 cells (see also Table 6). The specification teaches, that in view of this data, G1 cells can be selected and effectively used in NT methodology, and that G0 cells are not the only cell types that can be used in NT methods (p. 34, Conclusions).

State of the Art/ Predictability of the Art. The claims encompass cloning of primates, and in particular embodiments, humans (see claims 16 and 19, for example), which is found to be unpredictable for specific reasons. Vogel [**Science**, 300:226-227 (2003)] state that Rhesus monkey nuclear transfer (NT)-generated embryos seemed normal at their early stages but were unable to develop further when implanted into a surrogate mother. This was because the cells had the wrong number of chromosomes, and that this aneuploidy resulted in the abortion of the fetus. This was found to also be the case with human NT embryos. See p. 225. Simerly *et al.* [**Science**, 300:297 (2003)] state that, "Primate NT appears to be challenged by stricter molecular requirements than in other animals ... With current approaches, NT to produce embryonic stem cells in nonhuman primates may prove difficult · and reproductive cloning unachievable." See p. 297, 3rd column, last sentence. As the state of the art evidences, NT in primates is unpredictable, and the instant specification fails to provide teachings to show that primate NT using the claimed methods would result in pluripotent mammalian cells, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

The claims broadly encompass using any enucleated recipient cell for

methods of NT. Claims 14 and 15 are directed to enucleated stem cells, or a clump of enucleated stem cells fused together, and further embodiments state that the stem cells are embryonic stem cells. The specification provides no guidance with regard to utilizing, for its breadth, any recipient cell (which includes differentiated cells, adult, fetal or embryonic cells), any stem cell (which include pluripotent, multipotent and totipotent stem cells), or embryonic stem cells, for use in NT methods. One of skill could not rely upon the state of the art for guidance in utilizing any of these cell types in successful NT methods. The unpredictable state of the art of NT is supported by Campbell [**Cloning & Stem Cells**, 3(4):201-208 (2001)] state that, "Successful development [of the NT unit] is dependent upon numerous factors, including type of recipient cell, source of recipient cell, method of reconstruction, activation, embryo culture, donor cell type, and donor and recipient cell cycle stages." See *Abstract.* Campbell teaches that metaphase II [MII] oocytes are considered the cytoplast of choice because the genetic material is arranged upon the meiotic spindle and easily removed [see p. 202, 2nd column, 1st ¶], further, following introduction of the donor somatic cell into an enucleated oocyte, activation must occur to induce further development and the timing of this activation in relation to NT has been implicated in the ability of the NT unit to develop further [see p. 203, 2nd col.]. Fulka *et al.* [**Theriogenology**, 55(6):1373-1380 (2001)] state that the three basic types of cytoplasts 1) enucleated metaphase II oocytes that are used immediately for NT, 2) MII oocytes that are enucleated and aged in culture to be used in NT and 3) oocytes that are first activated and then enucleated in telophase II before use in NT. See p. 1374. Accordingly, the state of the art supports that only oocytes in MII or oocytes in telophase II be used for successful NT. The specification fails to provide guidance for the breadth of cells encompassed by the claims, including differentiated cells, to be used as recipient cells in NT methods.

The claims fail to provide a step of activating the resulting NT unit; thus, without further development of the NT unit, it would not be possible to generate a pluripotent cell. Indeed, the step of activating the NT unit is essential; Dinnyés *et al.* [**Cloning & Stem Cells**, 4(1): 81-90 (2002)] state that, "In NT, the lack of sperm-induced fertilization steps necessitate the application of an artificial activation in order to trigger further development." See p. 83, 2nd column, last ¶. Dinnyés state that, "NT is a complex procedure, and each step affects the overall efficiency. The unpredictability of the technology due to biological variation of the recipient oocytes and donor cells is difficult to control. Therefore, standardization of steps is important in order to obtain consistent results. Improvements in technical steps may have lasting effects on the development of the fetus." See p. 83, 1st column, 2nd full ¶. The instant claims fail to provide steps of activation or further culture of the NT unit and thus, in view of the state of the art, it would not be predictable that the resulting unit would be able to develop further.

Additionally, the claims fail to be enabling because they do not provide a step of transferring the resulting embryo into a surrogate mother of the same species. The state of the art of implanting embryos into surrogate mothers of different species is unpredictable. For example Fehilly *et al.* (**Nature**, Vol. 307, 16 February 1984) teach that often two unrelated species cannot carry a live hybrid fetus to term due to factors such as interspecific pregnancies, placental abnormalities and maternal immunological reaction against foreign antigens of the conceptus which would be the cause of immediate abortion (see p. 634, 1st column, 2nd paragraph). Fehilly *et al.* summarize experiments for the production of such animals, and show an extremely low percentage of full term young (see Table 1, p. 635). Although Fehilly *et al.* show that is possible to produce embryos that have been implanted into surrogate mothers of a foreign species, it is clearly an unpredictable process.

The Amount of Experimentation Necessary. The breadth of the claims is directed to cloning any non-human mammal by NT methods, using any donor cell with any recipient cell. However, the state of the art only supports utilizing an enucleated oocyte as a recipient cell, and because certain embodiments of the claims require production of a live born animal, the surrogate mother and recipient embryo must be of the same species.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to the production of the breadth of any animal, including primates, the lack of teachings or guidance with regard to the use of any recipient cell, other than an enucleated oocyte, the state of the art with regard to the unpredictability in producing cloned primates, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 9, 13, 17, 23, 29-32, 59-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is unclear. The metes and bounds of the claim cannot be determined, because it recites that the donor cell is in one or more known or unknown stages of the cell cycle. It is unclear what is encompassed by unknown stages of the cell cycle – that there is a stage of the cell cycle that is unknown, for example, a stage that has yet to be discovered, or that the cells are in an undetermined stage, because they have not been tested?

Claim 9 is unclear. The claim refers to "adult or fetal fibroblasts or follicular cells" it is unclear if the term "adult or fetal" refers to simply the fibroblasts, or both cell types.

Claim 13 is unclear. The claim recites that the oocyte is obtained from a species corresponding in origin to the donor nuclei. The metes and bounds of the phrase "corresponding in origin" cannot be determined, as it is unclear how the oocyte's species corresponds to the donor nucleus' species.

Claim 13 recites the limitation "the donor nuclei" in line 2. There is insufficient antecedent basis for this limitation in the claim. The claim refers to claim 12, which in turn, refers to claim 1, which only recites a single nucleus in step (b). Claims 59-62 depend from claim 13.

Claim 17 recites the limitation "the donor nuclei" in line 1. There is insufficient antecedent basis for this limitation in the claim. The claim refers to claim 16, which only recites a single donor nucleus.

Claim 21 is confusing because it recites that the embryo "comprises a transgenic embryo." The metes and bounds of this are unclear. Although the embryo can be transgenic, it cannot comprise another embryo.

Claim 23 is unclear. The claim recites that the embryo "comprises a species of mammal". The embryo can be a particular species of mammal, but it cannot comprise a mammal. The claim is further confusing. The metes and bounds of the claim cannot be determined because of the following: the claim recites a "non-human" animal embryo, but then lists that the mammal can be selected from a group comprising primates including humans. This contradicts the term of "non-human".

Claim 29 is unclear. The claim recites that the cloned non-human animal "comprises a mammal". It is unclear how an animal can comprise a mammal. Although the animal can be a mammal, the term "comprises" can encompass, for example, an animal that is pregnant with a mammal, or an animal that has ingested a mammal.

Claim 30 is similarly unclear because it recites that the cloned non-human animal comprises a transgenic non-human animal. Claims 31-32 depend from claim 30.

Claim 31 is similarly unclear because it recites that the cloned non-human animal comprises a transgenic bovine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 22, 23, 28, 29 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by McLaughlin *et al.* (**Reprod. Fertil. Dev.**, 2: 619-622 (1990)).

The claims are directed to a reconstituted non-human embryo (claim 20), wherein the embryo undergoes serial nuclear transfer (claim 22), wherein the species of embryo is selected from the group comprising primates, including humans, rodents, rabbits, cats, dogs, horses, cattle, sheep, sheep, deer goats, and pigs (claim 23), a cloned non-human animal (claim 28), selected from the group consisting of non-human primates, rodents, rabbits, cats, dogs, horses, cattle, sheep, deer (claim 29); offspring/descendents of the cloned non-human anima (claim 33).

The claims are product by process claims. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently

possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

The claims are interpreted as follows: a cloned embryo or animal, is indistinguishable from a naturally occurring animal. Similarly, offspring or descendents of a cloned animal are indistinguishable.

McLaughlin *et al.* teach sheep embryos (see Abstract, and Materials & Methods). They teach recipient ewes (p. 620, Results, 1st paragraph). Thus, McLaughlin *et al.* anticipate the claims, because they teach sheep embryos and sheep.

Claims 20-23, 28-30, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Schnieke *et al.* (**Science**, 278: 2130-2133 (19 December 1997)).

The claims are product-by-process claims (see above). The claims are not distinguished from transgenic animals that are made by different processes. The non-transgenic animals are not distinguished from naturally occurring animals.

Schnieke *et al.* teach the production the production of sheep embryos by nuclear transfer, wherein the fibroblast donor cells were co-transfected with a neomycin resistance marker and the human coagulation factor IX genomic construct (see Abstract and p. 2130, 1st column, 1st paragraph). They teach that the embryos were then transferred to surrogate mothers and live lambs were produced (p. 2131, 1st column, 3rd ¶). Thus, Schnieke *et al.* anticipate the claimed invention, because they teach transgenic sheep embryos and transgenic lambs. They anticipate the non-transgenic claims, because they teach ewes that were used to gestate the transgenic lambs (see, for example, Table 2 and pages 2131-2132, bridging ¶) and they teach non-transfected embryos (see Table 1).

Claims 20-23, 28-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Bowen *et al.* (**Biol. of Reprod.** 50:664-668 (1994)).

The claims are product-by-process claims (see above). The claims are not distinguished from transgenic animals that are made by different processes. The non-transgenic animals are not distinguished from naturally occurring animals.

Bowen *et al.* teach the production of transgenic embryos by microinjection of DNA (see Abstract and Embryo Manipulation, p. 664). They teach that the embryos were assayed to determine if they were transgenic or not (see Abstract). They teach that 112/533 embryos were transgenic. These transgenic embryos were then transferred to recipient cows, and resulted in the birth of a transgenic calf. See Abstract. Thus, Bowen *et al.* anticipate the claims, because they teach transgenic embryos, non-transgenic embryos, cows (which are surrogate mothers) and a transgenic calf.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5-13, 16-33, 56, 59-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell *et al.* (**WO 97/07668** (published 6 March 1997)) when taken with Boquest *et al.* (**Biol. of Reprod.**, 60: 1013-1019 (1999)), in further view of Alberts *et al.* (**Mol. Biology of the Cell**, 3rd Ed. 1994, Garland Publishing, Inc., NY, pages 903-904).

The claims are directed to methods of nuclear transfer, comprising selecting and segregating G1 cells from a proliferating or non-proliferating population of donor cells; and b) transferring a nucleus from the cell into an enucleated recipient cell. Specific embodiments limit the donor cells to either embryo, fetal, juvenile or adult cells, utilizing karyotypically normal cells; the cells are in an undifferentiated state, at any degree of differentiation, or quiescence, or senescence. The claims are further directed to utilizing adult or fetal fibroblasts or follicular cells, wherein the cells are modified, and particularly transgenic cells. The claims further limit the recipient cell to an enucleated oocyte, wherein the oocyte is from a species corresponding in origin to the donor nuclei. The claims are directed to methods of producing cloned animal embryos, wherein the embryos can be genetically altered, embryos and animals produced by these methods.

Campbell *et al.* teach methods of reconstituting an animal embryo, by transferring a diploid nucleus into an enucleated oocyte. They teach that the diploid nucleus can be in either the G0 or G1 phase of the cell cycle at the time of transfer. See Abstract. They teach that reconstructed embryo ploidy can be maintained by transferring nuclei at a defined cell cycle stage, such as

cells that are in G1 (p. 4, lines 2-4; p. 7, lines 19-21). They teach reconstituting animal embryos by methods of nuclear transfer (NT) and then subsequently transferring the embryo to a surrogate mother to produce a live-born animal (p. 5, lines 1-10). They further teach that the resultant animal can then be bred to produce offspring (page 15, lines 19-27; page 18, lines 18-22). They teach that these methods can be used in a variety of animal species, including those instantly claimed (p. 5, lines 14-27). They teach that the methods can be used to produce transgenic animals, by use of transgenic cells (p. 5, lines 30-33), and that the term "transgene" encompasses endogenous genes that are deleted, duplicated, activated, modified, or the addition of an exogenous DNA sequence (pages 5-6, bridging ¶). They teach that the donor cells that can be used in the NT methods include fully or partially differentiated cells, or undifferentiated cells that are either cultured *in vitro* or *in vivo*. They teach that these donor cells must be karyotypically normal. See page 8, lines 15-19. They teach that in order to produce increased yield of viable embryos, serial nuclear transfer rounds can be performed (p. 16, lines 9-13). They specifically teach examples of producing cloned bovine embryos utilizing nuclear transfer. They teach an enucleated oocyte from a cow (see Example 1, pages 21-22) and the reconstruction of bovine embryos using primary fibroblasts that are synchronized at the G0 phase of the cell cycle by serum starvation (see pages 25-26, bridging ¶). They also teach the enucleation of ovine (sheep) oocytes (Example 2) using an embryo-derived established cell line (see p. 27, lines 6-7).

Campbell *et al.* do not teach selecting and segregating G1 cells from a population of proliferating and non-proliferating donor cells, and they do not teach that the donor cell population comprises synchronized at any point in the G1 stage of the cell cycle. However, prior to the time the claimed invention was filed, Boquest *et al.* taught flow cytometric cell cycle analysis of

cultured porcine fetal fibroblasts. They particularly investigated the cell cycle characteristics of the fibroblasts, and discuss their results with regard to nuclear transfer methods. In particular, they state that, "In a quest to improve donor nuclei treatment prior to nuclear transfer, the present study was undertaken to examine the cell cycle characteristics of porcine fetal cells when cultured under a variety of cell cycle arresting treatments." See p. 1013, 2nd col., 3rd ¶. They teach flow cytometry to measure cellular DNA and protein content for various stages of the cell cycle, including G1. See page 1014, 1st column, Flow Cytometry and Confocal Microscopy and Figure 1, which shows both G0 and G1 cell populations, and the capability of distinction between G0 and G1 by protein content.

Neither Campbell *et al.* nor Boquest *et al.* explicitly teach that the donor cell population is non-proliferating and comprises senescent cells (claim 5), however, prior to the time of the claimed invention, Alberts *et al.* teach that senescent cells are cells that exit the cell cycle into G0 and never re-enter. They teach that cells stop dividing after a certain number of cycles, and for example, fibroblasts taken from animals with shorter lifespan cease to divide after a smaller number of divisions, when compared with cells from an animal with a longer lifespan (see pages 903-904, bridging sentence). Thus, because Campbell *et al.* suggest using G1 cells, and Boquest *et al.* provide a mechanism to segregate G0 cells from G1 cells in a mixed cell population, and further, because both Campbell *et al.* and Boquest *et al.* suggest using cultured fibroblast cell lines, one of skill in the art would reasonably expect that, in using a fibroblast cell line for a nuclear donor cell, some of the cells in that population would comprise senescent cells.

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art, to modify the teachings of Campbell *et al.* to isolate a G1 cell, as taught by Boquest *et al*, to use as a nuclear donor in NT methods, with a reasonable expectation of success. One of ordinary skill in

the art would have motivated to do this, as stated by Campbell *et al.*, that donor nuclei can be in the G1 phase of the cell cycle, and Boquest *et al.*, who state, "It is concluded that cell cycle analysis will enable the optimization of donor nuclei treatment, which should lead to improvements in the efficacy of nuclear transfer procedures." See p. 1018, 2nd column, 1st ¶, last sentence.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3, 4 and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell *et al.* when taken with Boquest *et al.* and further in view of Prather *et al.* (**Cloning**, 1(1): 17-24 (March 1999)), Gadbois *et al* **PNAS**, 89: 8626-8630 (September 1992) and Collas *et al.*(**Biol. of Reprod.**, 46:492-500 (1992)).

Claim 3 is further directed to synchronizing the donor cells at any point in the G1 stage of the cell cycle; claim 4 is directed to segregating an early G1 phase cell; claims 64-66 are directed to segregating a population of early G-1 phase from a population of early G1 phase-synchronized, non-proliferating cells.

Campbell *et al.* teach methods of reconstituting an animal embryo, by transferring a diploid nucleus into an enucleated oocyte. They teach that the diploid nucleus can be in either the G0 or G1 phase of the cell cycle at the time of transfer. See Abstract. They teach that reconstructed embryo ploidy can be maintained by transferring nuclei at a defined cell cycle stage, such as cells that are in G1 (p. 4, lines 2-4; p. 7, lines 19-21). They teach reconstituting animal embryos by methods of nuclear transfer (NT) and then subsequently transferring the embryo to a surrogate mother to produce a live-born animal (p. 5, lines 1-10). They further teach that the resultant animal can then be bred to produce offspring (page 15, lines 19-27; page 18, lines 18-22). They teach that these methods can be used in a variety of

animal species, including those instantly claimed (p. 5, lines 14-27). They teach that the methods can be used to produce transgenic animals, by use of transgenic cells (p. 5, lines 30-33), and that the term "transgene" encompasses endogenous genes that are deleted, duplicated, activated, modified, or the addition of an exogenous DNA sequence (pages 5-6, bridging ¶). They teach that the donor cells that can be used in the NT methods include fully or partially differentiated cells, or undifferentiated cells that are either cultured *in vitro* or *in vivo*. They teach that these donor cells must be karyotypically normal. See page 8, lines 15-19. They teach that in order to produce increased yield of viable embryos, serial nuclear transfer rounds can be performed (p. 16, lines 9-13). They specifically teach examples of producing cloned bovine embryos utilizing nuclear transfer. They teach an enucleated oocyte from a cow (see Example 1, pages 21-22) and the reconstruction of bovine embryos using primary fibroblasts that are synchronized at the G0 phase of the cell cycle by serum starvation (see pages 25-26, bridging ¶). They also teach the enucleation of ovine (sheep) oocytes (Example 2) using an embryo-derived established cell line (see p. 27, lines 6-7).

Campbell *et al.* do not teach selecting and segregating G1 cells from a population of proliferating and non-proliferating donor cells, and they do not teach that the donor cell population comprises synchronized at any point in the G1 stage of the cell cycle. However, prior to the time the claimed invention was filed, Boquest *et al.* taught flow cytometric cell cycle analysis of cultured porcine fetal fibroblasts. They particularly investigated the cell cycle characteristics of the fibroblasts, and discuss their results with regard to nuclear transfer methods. In particular, they state that, "In a quest to improve donor nuclei treatment prior to nuclear transfer, the present study was undertaken to examine the cell cycle characteristics of porcine fetal cells when cultured under a variety of cell cycle arresting treatments." See p.

1013, 2nd col., 3rd ¶. They teach flow cytometry to measure cellular DNA and protein content for various stages of the cell cycle, including G1. See page 1014, 1st column, Flow Cytometry and Confocal Microscopy and Figure 1, which shows both G0 and G1 cell populations, and the capability of distinction between G0 and G1 by protein content.

Neither Campbell *et al.* nor Boquest *et al.* specifically teach synchronizing the donor cells at any point in the G1 stage of the cell cycle, or particularly, in early G1. However, Prather *et al.* teach methods of synchronizing porcine cells, to be used in nuclear transfer, using mimosine (see Abstract, and p. 20, 1st col., 1st paragraph). They teach that the cells can then be identified using flow cytometry (p. 20, Results and p. 18, 2nd column). They teach that cells in G1 can be based upon both DNA content, and protein content (p. 18, 1st column, 1st ¶, lines 4-7. Prather *et al.* do not specifically teaching that the isolated cells are arrested in early G1, however, Gadbois *et al.* teach methods of arresting cells in early G1, utilizing staurosporine (see Abstract and p. 8627, 1st column, Kinase Inhibitor Studies).

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to isolate an early G1 cell from a population of donor cells, to use in methods of nuclear transfer, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification, as supported by Collas *et al.*, who show that utilizing early G1 phase cells in NT methodologies, found an enhanced rate of development in the resultant NT embryos. See Abstract and p. 493, 1st paragraph, last sentence, which states, "The results indicate that the extent of development *in vitro* was reduced as donor nuclei progressed in the cell cycle. The use of donor blastomeres in the G1 phase thus dramatically improved development of nuclear transplant embryos *in vitro*."

Note that Collas *et al.* is not used in this rejection with regard to their teachings of using G1 blastomeres in nuclear transfer, because the instantly-

filed specification explicitly excludes utilizing donor cells from blastomeres that are synchronized using nocodazole or colcemid (see p. 5, lines 17-20), which is the method, as taught by Collas *et al.* Collas *et al.* provide motivation with regard to utilizing G1 cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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thaian ton

Thaian N. Ton
Patent Examiner
Group 1632